L1 retrotransposition in human neural progenitor cells.

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Public Summary:
Long INterspersed Element-1 (LINE-1 or L1) is an abundant retrotransposon that comprises ~17% of human DNA. The average human is estimated to contain ~80-100 active L1s, and their mobility (i.e., retrotransposition) continues to impact the genome. L1 must retrotranspose in either the germ-line or during early development to ensure its evolutionary success; however, the extent to which this process impacts somatic cells remains an open question. We previously showed that an engineered human L1 can retrotranspose in rat neural progenitor cells (NPCs) in vitro and in somatic cells of the mouse brain in vivo. Here we demonstrate that NPCs isolated from human fetal brain and NPCs derived from human embryonic stem cells (hESCs) support the retrotransposition of engineered human L1s in vitro. Remarkably, we found that L1 retrotransposition can occur at relatively high levels in hESC-derived NPCs; characterization of the resultant retrotransposition events reveals that L1s frequently insert into or near genes. We also developed a quantitative assay that revealed an increase in the copy number of endogenous L1s in the hippocampus and, to a lesser extent, in the cerebellum of adult human brains when compared to the copy number of endogenous L1s in heart or liver genomic DNAs isolated from the same individual. Together, these data suggest that de novo L1 retrotransposition events may occur in the human brain and thereby contribute to individual somatic mosaicism.

Scientific Abstract:
Long interspersed element 1 (LINE-1 or L1) retrotransposons have markedly affected the human genome. L1s must retrotranspose in the germ line or during early development to ensure their evolutionary success, yet the extent to which this process affects somatic cells is poorly understood. We previously demonstrated that engineered human L1s can retrotranspose in adult rat hippocampus progenitor cells in vitro and in the mouse brain in vivo. Here we demonstrate that neural progenitor cells isolated from human fetal brain and derived from human embryonic stem cells support the retrotransposition of engineered human L1s in vitro. Furthermore, we developed a quantitative multiplex polymerase chain reaction that detected an increase in the copy number of endogenous L1s in the hippocampus, and in several regions of adult human brains, when compared to the copy number of endogenous L1s in heart or liver genomic DNAs from the same donor. These data suggest that de novo L1 retrotransposition events may occur in the human brain and, in principle, have the potential to contribute to individual somatic mosaicism.